REMARKS

Applicants would first like to thank Examiner Jeffrey Fredman for granting applicants a brief telephone interview on January 26, 2004. Claims 1-10, 13, 15, 30-33, 36 and 43-50 were pending in the subject application. Applicants have amended claims 1, 2-6 and 36 to provide proper antecedent basis. Applicants submit that this amendment does not introduce any new matter, and respectfully request entry of this amendment such that claims 1-10, 13, 15, 30-33, 36 and 43-50 will be pending.

Double Patenting Rejection

The Office Action rejects claims 1-10, 13, 15, 30-33, 36, and 43-50 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-10 of U.S. Patent No. 5,834,188. In response, without conceding the correctness of this rejection, Applicants are submitting a suitable terminal disclaimer to obviate this ground of rejection.

Since the Office Action does not set forth any grounds of rejection with respect to claims 4, 5, 7, 8, 10, 15, 30-33 aside from the obviousness-type double patenting rejection, these claims are expected to be deemed allowable by the Examiner, or allowable if rewritten to include all the elements of the base claim and any intervening claims, upon the filing of the enclosed terminal disclaimer. Accordingly, applicants respectfully request withdrawal of this ground of rejection and allowance of claims 4, 5, 7, 8, 10, 15, and 30-33.

Claim Rejections - 35 USC § 102

Applicants note for the record that the Examiner has withdrawn the previous novelty rejection with respect to claims 1, 13, 36, 45-47, 49 and 50 are novel over Harris et al. (U.S. Patent 6,083,690). Accordingly, the Examiner has conceded that these claims are novel over Harris.

Claim Rejections - 35 USC § 103

Applicants note, for the record, that the Examiner has withdrawn the previous obviousness rejection with respect to claims 1, 13, 36, 43, 45-47, 49 and 50 over Harris et al. in view of Smart

(U.S. Patent 5,650,276). Accordingly, the Examiner has conceded that these claims are nonobvious over Harris in view of Smart.

While conceding that the pending claims are novel and nonobvious over Harris in view of Smart, the Examiner rejects claims 1-3, 6, 9, 13, 36, 43-47, 49 and 50 under 35 USC § 103 as allegedly unpatentable over Harris in view of Smart and in further view of Nadal-Ginard (WO94/18239).

As a preliminary matter, applicants respectfully note that the Office Action is internally inconsistent. The Examiner has reproduced his previous rejection providing reasons why claims 1-3, 6, 9, 13, 36, 43-47, 49 and 50 are allegedly obvious over Harris in view of Smart, even though the Examiner has conceded that these claims are not obvious over Harris and Smart. As an example, the Office Action states on page 6, of the response, that "Harris in view of Smart teach all the limitations of claims 1, 13, 36, 43, 45-47, 49 and 50 as discussed above" while withdrawing this very same rejection on page 3, lines 5-7 of the Office Action.

Furthermore, Applicants respectfully draw the Examiner's attention to MPEP 706.07, which requires that all outstanding grounds of rejection be clearly developed by the Examiner so that applicants may readily judge the advisability of appeal:

> In making the final rejection, all outstanding grounds of rejection of record should be carefully reviewed, and any such grounds relied on in the final rejection should be reiterated. <u>They must also be clearly developed to such an extent that applicant may readily judge the advisability of an appeal</u> unless a single previous Office action contains a complete statement supporting the rejection. (Emphasis added).

Applicants respectfully submit that the Examiner has not clearly developed the new grounds of rejection under 35 USC §103. For example, rather than setting forth a prima facie case of obviousness with respect to Harris/Smart/Nadal-Ginard as they relate to claim 1, the Examiner has merely reiterated on pages 3-8 of the office action the previous arguments for rejecting claim 1 based on the alleged teachings of Harris and Smart only, thereby unfairly burdening applicants is assessing the advisability of appeal.

In addition, MPEP 706.02(j) requires, among other things, that the prior art references teach or suggest all the claim elements in order to establish a *prima facie* case of obviousness. Applicants respectfully submit that the Examiner has not provided any rationale as to why Nadal-Ginard, in combination with Harris and Smart, teaches all the features of claim 1. Rather, pages 3 to 8 of the Office Action appear to be an almost exact reproduction of the rejection in the previous Office Action rejecting claim 1 on the basis of Harris and Smart only, and not on the basis of Harris, Smart and Nadal-Ginard. The Examiner, while conceding that Harris and Smart do not teach all the elements of claim 1, has failed to show in the Office Action how these references in view of Nadal-Ginard fail to overcome this deficiencies of Harris and Smart.

A similar deficiency is evident with respect to Ozkaynak. The Examiner rejects claims 1, 13, 36, 43 and 45-50 under 35 U.S.C. 103(a) as being unpatentable over Harris in view of Smart and further in view of Ozkaynak, yet page 8 of the Office Action merely reproduces the Examiner's previous argument as to how Ozkaynak teaches the features of dependent claims reciting N-CAM. The Examiner does not show how the three references teach the elements of claim 1.

Failure of references to teach all claim limitations

As stated above, MPEP 706.02(j) requires, among other things, that prior art references must teach or suggest all the claim elements in order to establish a *prima facie* case of obviousness.

Applicants first submit that the Harris does not teach all the elements of claims 1 and 36. For Example, Harris teaches response elements from the promoters of morphogen genes themselves *i.e.* transcription response elements that are present in the DNA sequences of morphogen genes such as those from the mouse BMP-4A gene; Harris however does not describe transcription response elements from downstream genes which are regulated by morphogens *i.e.* genes that are downstream in the signal transduction pathway.

Accordingly, applicant's claimed invention is distinct from the teachings of the cited patent: applicant's claims recite methods of identifying agents based on their ability to induce expression of a reporter gene, where the reporter gene is operably-linked to a transcription response element from a gene whose expression is regulated by a morphogen; in contrast, Harris relates to the identification of agents based on their ability to induce expression of a reporter gene that is operably-linked to a transcription response element of a morphogen gene itself.

Column 4, lines 32-42 of Harris make this point very clear, reciting as follows:

> The present invention is distinguished from other techniques for identifying bone-active compounds, as it specifically identifies chemical compounds, agents, factors or other substances which stimulate bone cells to produce the bone growth factors in the bone morphogenetic protein (BMP) family (hereinafter "osteogenic agents"). These osteogenic agents are identified by their capacity to increase the activity of the promoters of genes of members of the BMP family and other bone growth factors which are normally produced by bone cells, and other cells including cartilage cells, tumor cells and prostatic cells. (Emphasis added).

Harris further states on column 2, lines 33-40, as follows:

> Also provided in accordance with the present invention are isolated DNA sequences encoding a promoter region of at least one bone morphogenetic protein, and a system for identifying osteogenic agents comprising an expression vector comprising such promoter sequences operatively linked to a reporter gene encoding an assayable product, and means for detecting the assayable product produced in response to exposure to an osteogenic compound. (Emphasis added).

In contrast, Applicants' claims 1 and 36 recite the transcription response elements of the downstream genes which morphogen proteins regulate, not promoter regions or transcription response elements from morphogen genes. Thus, Harris fails to teach or suggest all the claim elements, and in particular fails to teach a screening method using a downstream transcription activating element that is responsive to the morphogen as recited in the claims 1 and 36, from which claims 13, 45-47, 49 and 50 depend.

Not only does Harris fail to teach every element of claim 1, Smart fails to correct this deficiency. Smart describes methods of screening candidate compounds for the ability to modulate the level of a morphogenic protein. The teachings of Harris and Smart are both limited to identifying agents which regulate the gene expression of morphogen genes: Harris at the level of transcription from the promoter of morphogen genes and Smart at the level of morphogen proteins. However, the combined teachings of Harris and Smart are completely silent as to the use of transcription activating element from genes that are responsive to, and distinct from the gene encoding, the morphogens.

In addition, Smart teaches away from the claimed invention by reinforcing the teachings of Harris. Like Harris, Smart teaches measuring gene expression of the morphogen as the focal point of the drug screening assays, and not the use of genes downstream of the morphogen. Moreover, applicants note that on pages 5-6, bridging paragraph of the Office Action, the Examiner states that Smart teaches (a) a method of screening candidate compounds for the ability to modulate the effective local or systemic concentration or level of a morphogenic organism; and (b) the desirability of screening candidate compounds for their ability to modulate morphogenic proteins. Accordingly, it appears that the Examiner himself concedes that Smart relates to identifying compounds which regulate the expression of morphogen genes rather than agents which modulate the gene expression of downstream genes.

Harris, Smart and Nadal-Ginard

Not only does Harris in view of Smart fail to teach every element of claim 1, Nadal-Ginard fails to correct this deficiency *i.e.* Harris in view of Smart in further view of Nadal-Ginard fail to teach all the claim elements of claim 1. The examiner, while conceding that Harris and Smart do not teach every element of claim 1 as evidenced by his withdrawing the obviousness rejection based on Harris/Smart, has failed to articulate how the Nadal-Ginard rectifies this deficiency.

Harris in view of Smart and in further view of Nadal-Ginard fails to teach a method for

identifying a compound that induces a morphogen-mediated biological effect using a downstream transcription activating element that is responsive to the morphogen as recited in the pending claims. First, Nadal-Ginard fails to teach a transcription activating element that is responsive to a morphogen, either on its own or in view of Harris and Smart. In fact, applicants were unable to find any reference in Nadal-Ginard that relates to a morphogen *i.e.* no references to morphogen proteins, morphogen receptors, morphogen genes, biological activity of morphogens, or transcription activating elements that are responsive to morphogens. Second, Nadal-Ginard does not teach, either on its own or in view of Harris and Smart, screening assays for identifying agents that induce the biological effect of a growth factor, let alone a morphogen as recited in claims 1 and 36. Rather, the teachings of Nadal-Ginard, even in view of Harris and Smart, teach at best, a method of identifying agents which modulate the physical interaction between a pocket protein and a tissue specific transcription factor. Accordingly, since the combined teachings of Harris, Smart and Nadal-Ginard fail to teach every element of claims 1 and 36, the fail to render obvious the claimed invention.

The Office Action alleges the following on page 9, third paragraph:

> ...Nadal-Ginard expressly teaches "The agent can affect e.g. induce or enhance, the expression of a pocket protein. (See page 17, lines 20-21.) So Nadal-Ginard expressly teaches the new requirement of an agent, such as a morphogen, which induces the expression of a different protein. This is particularly exemplified in claim 4 of Nadal-Ginard, in which expression of a reporter construct that is dependent upon interaction of a candidate agent with the promoter sequence of a candidate agent with the promoter sequence of a downstream gene.

In response to this statement in the Office Action, applicants submit that, as stated previously, Nadal-Ginard does not teach, or even mention, morphogens. Accordingly, the statement that Nadal-Ginard teaches morphogens which induce the expression of a different protein appears unfounded. Applicants respectfully request that the Examiner point out which sections of Nadal-Ginard recite morphogens. Furthermore, applicants submit that claim 4 of Nadal Ginard, at best, relates to the use of a reporter gene operably linked to a gene or gene segment that is responsive to one of the transcription factors, but not to a transcription activating

element that is responsive to a morphogen. Furthermore, applicants submit that even if claim 4 of Nadal Ginard where to teach what the examiner alleges it teaches, which it does not, applicants submit that those teachings are not enabled by the specification because they do not describe how such elements would be used in a screening assay to identify compounds that induce a morphogen-mediated biological effect. In summary, the Examiner fails to show how Nadal-Ginard allegedly overcomes the deficiencies of Harris and Smart in teaching the claimed invention, and in particular, the use of a transcription activating element that is responsive to a morphogen in the screening methods.

Applicants further submit that even if Nadal-Ginard had described a transcription-regulatory element responsive to a morphogen, which applicants do not concede, Harris and Smart teach away from using such downstream activating elements, and instead teach using transactivating elements from morphogen genes themselves. Accordingly, one skilled in the art would not have been motivation to combine the teachings of Harris and Smart with those of Nadal-Ginard. Rather one would have been motivated to combine Harris and Smart with references that teach transcription activating elements found in morphogen promoters; however, such a combination does not render obvious the claimed invention obvious.

Harris, Smart and Ozkaynak

Not only does Harris in view of Smart and Nadal-Ginard fail to teach every element of claims 1 and 36, from which all other rejected claims depend, Ozkaynak also fails to correct the deficiencies of Harris and Smart *i.e.* Harris in view of Smart in further view of Ozkaynak fail to teach all the claim limitations of claims 1 and 36. The Examiner conceded that Harris and Smart do not teach every element of claim 1 by withdrawing the obviousness rejection based on Harris/Smart, and failed to articulate how Ozkaynak rectifies this deficiency *i.e.* has failed to show how Ozkaynak teaches a transcription activating element that is responsive to a morphogen.

The Office Action alleges that Ozkaynak teaches that morphogens induce CAM

expression, particularly N-CAM expression, as part of their induction of morphogenesis, and further alleges that "Ozkaynak teaches a downstream expression, here N-CAM, which is a promoter distinct from the gene encoding a morphogen" (page 9, lines 15-16).

In response, applicants submit that even if N-CAM was a gene whose expression is regulated by a morphogen, the Examiner has failed to show how Ozkaynak teaches a transcription activating element that is responsive to the morphogen. The examiner appears to assume that the N-CAM promoter is the transcription activating element that is responsive to the morphogen without providing any evidence that this is the case. Applicants submit that while Ozkaynak states that N-CAM is expressed in response to morphogens, it does not state that the N-CAM gene has a transcription activating element, does not indicate where such an hypothetical element would be located (e.g. which section of the promoter, intron, intergenic regions, etc.), and does not describe the sequence of the hypothetical element. Accordingly, the Office Action has failed to show that Ozkaynak teaches a transcription activating element that is responsive to the morphogen.

Applicants further submit that even if Ozkaynak had described a transcription activating element responsive to a morphogen, which applicants do not concede, Harris and Smart teach away from using such downstream activating elements, and teach instead the use of transcription activating elements from morphogen genes themselves. Accordingly, if one skilled in the art would had any motivation to combine the teachings of Harris and Smart with those of Ozkaynak, which applicants do not concede, the combined teachings suggest using it would be to use a transcription activating element from OP-3 itself to screen for agents which induce an OP-3-mediated biological effect. Applicants further submit that even if the Examiner were to cite a reference which teaches the sequence of a transcription activating element responsive to a morphogen, there would have been no motivation to combine Harris and Smart with such reference, since such sequence would not be that of a morphogen gene itself.

Additional Claim elements not taught by Harris, Smart and Nadal-Ginard/Ozkaynak

In addition to failing to teach the use of a transcriptional activating element in a screening assay, the combination of references cited in the Office Action fails to teach additional features of the pending claims. Claim 36 for example, recites "wherein step (c) occurs within approximately 2-12 hours of completing step (b)." However, the Office Action does not set forth how the combinations of references would allegedly teach this element of the claim invention. Likewise, claim 48 recites a method wherein "the morphogen-mediated biological effect is induction of mitogenesis and phenotypic markers for chondrocyte or osteoblast differentiation," but the Office Action fails to set forth how these morphogen-mediated biological effects are taught by the cited references. Accordingly, applicants respectfully submit that the Office Action has failed to set forth a prima facie case of obviousness for any of the claims, and in particular claims 36 and 48, and respectfully request withdrawal of this ground of rejection.

Entry of Amendment after Final

Applicants note that if entry of this amendment is not deemed by the Examiner to place the claims in immediate condition for allowance, it does place the claims in better condition for appeal according to MPEP 714.13(III), for example, by overcoming the double patenting rejection via the terminal disclaimer. Accordingly, applicant respectfully requests that this amendment be entered.

CONCLUSIONS

In view of the above amendment, applicants believes the pending application is in condition for allowance.

Applicants believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. JJJ-P02-540 from which the undersigned is authorized to draw.

Dated: February 22, 2005

Respectfully submitted,

By _____

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